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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,902	09/13/1999	Steven L. Stice	000270-026	5113

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/394,902	STICE ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,36,37,41,42,44,46,47 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34, 36, 37, 41, 42, 44, 46, 47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed 6/6/02, Paper No. 12, has been entered. Claims 35, 38-40, 43, 45 and 48 have been cancelled. Claims 1, 30-32, 36 and 41 have been amended. Claims 1-34, 36, 37, 41, 42, 44, 46, 47 and 49 are pending and under current examination.

Priority

The amendment to the priority information is proper and has been entered.

Oath/Declaration

The petition requesting that the declaration be accepted without the signatures of all the inventors, pursuant to 37 C.F.R. §1.47 (a) was granted on 8/17/01, Paper No. 7.

Double Patenting

The terminal disclaimers over U.S. Pat. No. 5,945,577 and 6,235,969 [Paper No. 17], is proper and has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34, 36, 37, 41, 42, 44, 46, 47 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cloning a porcine fetus or live offspring by transfer of a differentiated pig cell or a pig cell nucleus into *an enucleated pig oocyte*, to form a nuclear transfer unit, activating the nuclear transfer unit and transferring the cultured nuclear transfer unit into a female porcine, such that the nuclear transfer unit develops into a porcine fetus or live porcine and methods of producing a porcine CICM pluripotent cell line by nuclear transfer, the specification does not reasonably provide enablement for a method of cloning a porcine fetus or live offspring by nuclear transfer by inserting a desired differentiated pig cell or cell nucleus into an enucleated pig blastomere, under conditions suitable for the formation of a NT unit; removing the endogenous nucleus from the blastomere if not previously removed, activating the resultant NT unit, optionally culturing the NT unit and transferring the optionally cultured NT unit to a host female porcine such that the NT unit develops into a porcine fetus or animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a method of cloning a porcine fetus or live offspring, comprising inserting a desired differentiated pig cell or cell nucleus

into an optionally enucleated pig oocyte or blastomere under conditions suitable for the formation of a nuclear transfer unit, removing the endogenous nucleus from the oocyte or blastomere if not previously removed, activating the resulting nuclear transfer unit, optionally culturing the nuclear transfer unit, and transferring the cultured nuclear transfer unit into a female porcine such that the nuclear transfer unit develops into a porcine fetus or animal. In further embodiments, the claimed invention is directed to methods of producing a porcine CICM pluripotent cell line.

Applicants argue that with respect to using blastomeres, it appears that the significance of the 1992 Kato report, cited by the Examiner in the prior Office action, has been misconstrued. Particularly, Applicants argue that Kato describe the failure of mouse fetal germ cells to produce chimeric mice as being attributable to incompatibilities between the donor fetal germ cells and recipient blastomeres, rather than the inability of blastomeres to serve as recipient cells. Applicants submit that Johnson teach the embryogenic potential of blastomeres, wherein they describe separating the blastomeres of four-cell embryo, culturing them to form blastocysts, and implanting these into cows to produce four identical calves. Applicants further point to the teachings of Nakamura and Kono, who have shown that chimeric mice can be produced by transplanting a single nuclei of 2-8 cell embryos into an enucleated blastomere of a 2-cell embryo. Applicants further cite Niemann who report individual blastomeres of porcine 4-cell and 8-cell embryos can be cultured *in* vitro to the blastomere stage, and Chan who report that blastomeres

of primate embryos can be separated to produce identical twims and larger sets. See pp. 6-7 of Applicants' Response.

Applicants' arguments have been considered, however, they are not found to be persuasive. The art that Applicant has cited is not analogous to the instant invention because the invention requires nuclear transfer and the subsequent reprogramming of the differentiated pig cell or cell nucleus in order to effect development. The art cited by Applicant is not NT art, but art teaching the culturing blastomeres to form blastocysts, which can then be transplanted to recipient females, for example. The cited art does not address utilizing a blastocyst as a recipient cytoplast. The state of the art of recipient cytoplasts is taught by Campbell *et al.* [**Cloning & Stem Cells**, 3:201-208 (2001)] who state that, "Successful development (of an NT unit] is dependent upon numerous factors, including type of recipient cell, source of recipient cell, method of reconstruction, activation, embryo culture, donor cell type, and donor and recipient cell cycle stages." See *Abstract.* Campbell further teaches that oocytes, fertilized zygotes, and 2-celled embryos have been used as cytoplast recipients. They further state that, "The use of fertilized zygotes has been reported in mouse, cattle and pigs. In all three species, development of embryos reconstructed using zygotes as cytoplast recipients was low, and on the whole, restricted to the exchange of pronuclei, suggesting that factors essential for successful development are removed with the pronuclei." See p. 202, 2nd column. The importance of the type of cytoplast recipient in NT methods is further supported by Renard *et al.* [**Theriogenology**, 57:203-222

(2002)] who state that enucleated oocytes used in NT have various cytoplasmic cell cycle regulators, importantly, the maturation promoting factor [MPF] which is responsible for the induction of the remodeling of nuclear structure. Factors such as correct cell cycle synchronization between the cytoplast and karyoplast at the time the transplanted nuclei are exposed to MPF is essential. See p. 206 and Table 1. Moreover, Renard suggest that that different species have different timing of activation after transfer of the nucleus [see p. 207, 2nd ¶]. Although the specification provides guidance with regard to the use of an enucleated oocyte as a recipient for NT, the specification fails to teach or provide guidance for using an enucleated blastomere as a cytoplast recipient for NT. As such, one would have to rely on the state of the art with regard to cytoplast recipients used in NT. It is clear from the above-cited art that although it is established that an enucleated oocyte is successful in NT methods, other sources of cytoplast recipients are unpredictable, such as the zygotes the Campbell reference refers to, which states that development was low and restricted. The specification fails to provide guidance with particularity to show that an enucleated blastomere, as claimed, would be able to support the development of the NT unit such that it would develop into a porcine fetus.

Accordingly, in view of the unpredictable and undeveloped art of using enucleated blastomeres as cytoplast recipients in nuclear transfer and the lack of guidance or working examples provided by the specification for use of enucleated blastomeres in nuclear transfer, it would have required undue experimentation for

one skilled in the art to make and/or use the claimed porcine fetuses or live offspring, cell lines, and methods of using the same.

Claim Rejections - 35 USC § 112

The prior rejection of claims 30-32, 36 and 41-48 under 35 U.S.C. 112, second paragraph, is *withdrawn* in view of Applicants' arguments and/or amendments to the claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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